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Cadherins in tissue architecture and disease

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Abstract Cadherins are homophilic cell adhesion molecules that determine tissue architecture and control cell contact formation and dissociation in development and tissue homeostasis of all metazoans. These adhesion molecules mediate homophilic interactions between cells and are linked inside the cell via a complex set of cytosolic factors to the actin cytoskeleton. These interactions are key to the plasticity of intercellular junctions and to the various signaling functions of the cadherins. This forms the basis for cadherin-driven cell behavior, cell differentiation, and regeneration of tissue structures. Consequently, mutations in cadherins are the cause of various human pathologies, with cancer representing one of the most prominent examples.

Keywords Cell adhesion · Cadherins · Catenins · Junctions · Mechanotransduction · Cancer

Cell adhesion and cell-cell recognition are essential cellular functions that underlie tissue morphogenesis and the manifold dynamic cellular interactions of the immune system. The phenomenon of cell type-specific adhesion was established by demonstrating that cells from experimentally dissociated animal tissues can adhere to each other in specific ways and reform tissue-like structures [1]. At that time, theories for the formation of proper cell-cell contacts ranged from concepts of cell surface charge and van der Waals interactions that would be independent of certain cell surface macromolecules [2] to a chemoaffinity hypothesis postulating specific "cytochemical tags" for each combination of adhering cells [3].

Most strategies to identify cell adhesion molecules were based in the past on the use of antibodies that were able to inhibit cell adhesion in various experimental settings. Today, we know four major families of cell adhesion molecules: Cadherins were found as homophilic adhesion molecules that direct embryonic morphogenesis [4, 5]. Integrins are cell surface receptors for extracellular matrix proteins and can also directly mediate heterophilic cell-cell adhesion mainly between cells of the vascular system [6]. A third very large group of cell adhesion molecules (CAMs) belongs to the immunoglobulin superfamily best studied in the neuronal and the vascular system [7]. Finally, the most recently identified family of adhesion molecules are the selectins that are specialized for rapid adhesive events in the vascular system [8].

Identification of cadherins

Cell adhesive events mediated by cadherins were discovered by several groups who searched in parallel for the molecular identity of these cell adhesion molecules. Masatoshi Takeichi coined the name cadherins [9], and his group was the first to clone a full-length cDNA of a cadherin (E-cadherin) whose expression in cells conferred cell adhesion activity [10]. His group was also the first who identified with P-cadherin and N-cadherin additional members of this family (see below).

Two seminal findings were essential for the identification of the cadherins. First of all, it was found that hamster lung epithelial cells adhere to each other by Ca^{2+}-dependent and Ca^{2+}-independent mechanisms [11]. A technically important characteristic of these mechanisms was that they differed in their trypsin sensitivity, which allowed selective destruction of each mechanism on the cell surface, while the other mechanism was left intact. Low trypsin concentrations in the absence of Ca^{2+} destroyed selectively the Ca^{2+}-dependent adhesion mechanisms, whereas in the presence of Ca^{2+}, the Ca^{2+}-dependent adhesion mechanisms were protected, but the Ca^{2+}-

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independent mechanisms were destroyed by high trypsin concentrations. This facilitated the generation of polyclonal antibodies against cells enriched on their surface for Ca^{2+}-dependent adhesion molecules by pretreatment with high trypsin concentration in the presence of Ca^{2+}. However, the initially studied hamster epithelial cells were not well suited as immunogen to generate adhesion-blocking antibodies.

This is when a second discovery became important. Trying to elucidate the adhesion mechanisms that underlie the compaction of the early mouse embryo morula, Rolf Kemler generated polyclonal antibodies that were able to block compaction of the eight-cell stage mouse embryo (without inhibiting proliferation) and could even reverse compaction of later stage morulas [12]. These antibodies had been generated against the mouse embryonal carcinoma cell line F9. This serum was then later used to purify a 84-kD trypsin fragment of a cell surface protein from such cells, which was able to inhibit the cell adhesion-blocking effect of the antibodies [13]. Ca^{2+} protected the fragment from further degradation, and the postulated membrane protein from which this fragment was derived was called uvomorulin, with reference to the shape change of the morula [14].

The approach to use embryonal carcinoma cells as immunogen for adhesion-blocking antibodies was then used by the Takeichi group to generate partially purified polyclonal antibodies selectively recognizing cell surface proteins protected by Ca^{2+} from trypsin degradation. In this way, a membrane protein was found as a potential candidate for a Ca^{2+}-dependent adhesion molecule of these cells [15]. Generating monoclonal antibodies (mAb) against trypsin/Ca^{2+} treated F9-cells and screening the mAb for their ability to disrupt the monolayer of such cells gave rise to mAb ECCD-1 that defined a 120-kD cell surface protein with all the characteristics of the sought after adhesion molecule [9]. Since this antigen was also recognized by antibodies against uvomorulin and it was found not only on cells of the morula but also on epithelial cells of different embryonic tissues, it was suggested to change the name of the protein to cadherin [9]. The concept that a family of Ca^{2+}-dependent adhesion molecules exists that support cell type-specific adhesion was verified by identifying N-cadherin on neuronal cells, which led to the name E-cadherin for the epithelial cadherin [16]. Another cadherin was then identified in the mouse placenta, hence the name P-cadherin [17].

Uvomorulin/E-cadherin was also found by a differential screening approach aiming at identifying cell surface proteins specific for embryonal but not differentiated mouse carcinoma cells. In this way, a 120-kD protein was identified and purified by two-dimensional gel electrophoresis and immunization gave rise to an antiserum that turned out to block mouse embryo compaction, recognize the trypsin fragment of uvomorulin, and detect this protein on various adult epithelial cell types [18]. With the help of these antibodies, uvomorulin/E-cadherin was identified as a component of adherens junctions [19].

Other antibody-based approaches that defined E-cadherin in different species led to the identification of L-CAM on chicken hepatocytes whose homology to mouse E-cadherin was clarified by cloning [20]. Using MDCK cells, the canine homolog of E-cadherin was also defined by mAb anti Arc-1 [21] and mAb rr1 [22]. Finally, Cell-CAM 120/80 from human mammary carcinoma cells also shared all characteristics of E-cadherin [23].

Cadherin structure and classification

The first three identified cadherins, E-, P-, and N-cadherins, belong to the classical family of cadherins (type I). Today, many more cadherin and cadherin-related proteins have been identified in various species. The classical cadherins contain five typical extracellular cadherin (EC) domains, with a

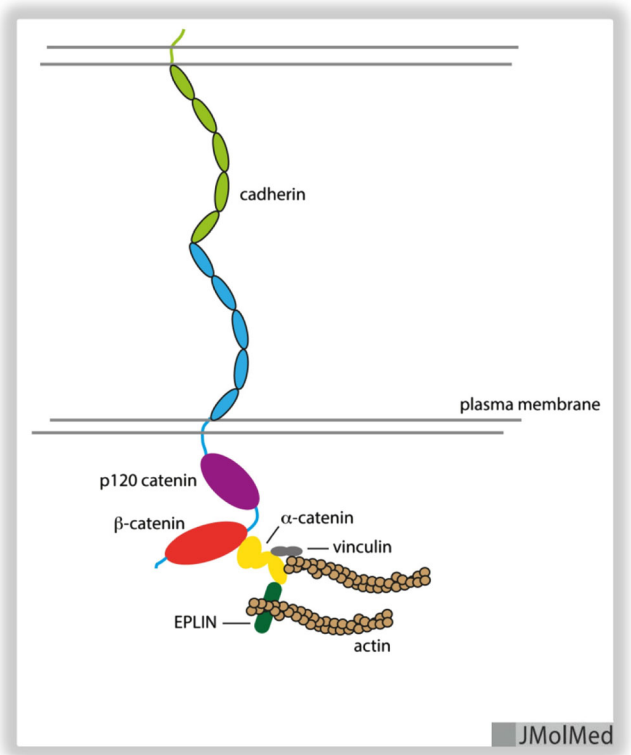

Fig. 1 Schematic drawing of a trans dimer of a classical cadherin, containing five extracellular cadherin (EC) domains. The intracellular domain binds with a juxtamembrane region to the catenin p120 and with a region closer to the C-terminus to β-catenin that links the cadherin to α-catenin. The latter anchors the cadherin to the actin cytoskeleton, an essential interaction for the cell adhesion function of cadherins. This interaction may either be direct or may be indirectly mediated by potential linkers such as EPLIN or vinculin. The latter binds to a site in α-catenin, whose accessibility is modulated by tension

barrel-like structure that resemble Ig-domains, although they share no sequence similarity to Ig family members [24]. Cadherins can interact in cis to form clusters and mediate adhesion via homophilic trans interactions. The N-terminal EC domain is of major importance for these interactions. The structural details of cadherin binding have been intensively analyzed, and different interfaces between the molecules were defined by crystallization of recombinant forms of different cadherins containing different numbers of EC domains. The crystal structure of C-cadherin from Xenopus (type I cadherin) containing all five EC domains revealed a slightly bent shape of the extracellular part of the protein, which allowed cis interactions via EC1 and EC2 of two adjacent molecules. Trans interactions relied on the mutual exchange of tryptophans at position 2 that insert into hydrophobic pockets of EC1 of the partner protein [25]. Attempts to confirm the EC1/EC2 cis interactions through solution-binding measurements did not succeed [26]. Additional binding interfaces such as an X dimer-based interaction of the EC1-EC2 junctions have been described and may be relevant as kinetic intermediates for the formation of cadherin trans dimers [26, 27]. Surprisingly, heterophilic interactions between different types of cadherins have been demonstrated with comparable binding parameters compared to homophilic interactions [28, 29].

Classical type II cadherins (at present 13 members) contain two tryptophans at positions 2 and 4. The most intensely studied member of this group is the endothelial specific VE (vascular endothelial)-cadherin [30]. It was originally thought that they might interact in structurally different ways than type I cadherins but the crystal structure of the first four domains of VE-cadherin (still fully glycosylated) revealed a very similar structure as that described for type I cadherins [31]. Type I and II classical cadherins, together with the desmosomal cadherins, form the large majority of the cadherin major branch [32]. More distantly related cadherins belong to the cadherin-related branch, like the protocadherins and others.

The classical cadherins and the desmosomal cadherins are differently anchored to the cytoskeleton. E-cadherin is a central constituent of adherens junctions of epithelial cells [19]. In contrast, the desmosomal cadherins which consist of desmocollin-1, desmocollin-2, and desmocollin-3 and desmoglein-1 to desmoglein-4 mediate the stability of desmosomes [33]. Adherens junctions are anchored to the actin cytoskeleton and are of central importance for the dynamics of cell contacts and establishment of cell polarity. Desmosomes are linked to intermediate filaments and represent junctions that are well suited to resist mechanical stress. Consequently, desmosomes and their cadherins are abundant in skin and heart.

The role of cadherins in mechanotransduction and junctional dynamics

Cadherins require anchoring to the cytoskeleton for proper adhesive function and junction organization (Fig. 1). This is mediated by the catenins, a class of cytosolic proteins that were identified as cadherin-associated proteins necessary for cell adhesion [34]. Catenins form a protein family that is characterized by the armadillo repeat. Cadherins bind with their C-termini to β-catenin that in turn binds to α-catenin. Additionally, alternative complexes are expressed where β-catenin is replaced by plakoglobin (γ-catenin). The essential role of α-catenin for the adhesive function of E-cadherin was demonstrated by re-expressing α-catenin in cells that lacked this catenin, which led to cell aggregation [35].

The cadherin catenin complex is connected via α-catenin with actin filaments, an interaction that may not be direct [36], and might require further bridging proteins such as epithelial protein lost in neoplasm (EPLIN) or vinculin [37, 38]. Indeed, tension at cellular junctions was shown to enhance the binding of vinculin to α-catenin, thereby stabilizing actin anchorage [38, 39]. Depending on the orientation of actin filaments towards the junctional interface, linear and punctate adherens junctions are distinguished. EPLIN is found at linear adherens junctions. Depletion of EPLIN leads to the disruption of such junctions and the formation of punctate junctions, which represent sites of high dynamics and tension [40]. While this study was performed with epithelial cells, EPLIN was also found to associate with VE-cadherin catenin complexes [41]. It is generally believed that the modulation of actin anchorage of the cadherin catenin complex is of central importance for the regulation of the dynamics of adherens junctions and cell contacts. Another aspect that is crucial for the control of cadherin function is lateral clustering in the membrane. This is thought to be important for the control of cell shape and for tissue morphogenesis [42]. Different myosin II isoforms are involved in the accumulation of E-cadherin at zonula adherens and in the local dynamics of actin filaments [43]. Mechanosensitive slowdown of actin turnover enhances E-cadherin recruitment at contact areas [44].

Another member of the catenins, p120, binds to a juxtamembrane site of the cytoplasmic part of cadherins. Binding of p120 inhibits constitutive cadherin endocytosis and thereby supports expression of cadherins at junctions [45]. In addition, p120 can regulate the activity of Rho family GTPases and can recruit the minus ends of microtubules to the cadherin complex.

The physiological roles of cadherins

Epithelial mesenchymal transition (EMT) converts epithelial cells into migrating mesenchymal cells and is usually

(although not in all examples) associated with downregulation of E-cadherin. This is a central process at numerous steps during embryonic development, such as gastrulation and neural crest cell delamination and also at later stages of embryonic development [46]. The reversed process mesenchyme-epithelial transition (MET) describes the condensation of mesenchymal cells and the formation of epithelia. This occurs multiple times during embryonic development and induction of E-cadherin in such structures is a hallmark of MET as was shown for the developing kidney [47]. During gastrulation, epithelial cells of the ectoderm in the region of the primitive streak undergo EMT; they detach from the cell layer and form later the mesoderm and the endoderm. The induction of transcriptional repressors such as the Snail factors (and others) inhibits the expression of E-cadherin and supports EMT [46].

Neural crest cells (NCC) develop from a specialized (N-cadherin expressing) area of the epithelial cells of the neuroectoderm, from where they detach after downregulation of N-cadherin and migrate to various target sites where they differentiate to specialized cells such as neurons and glia, craniofacial tissues, and melanocytes. N-cadherin is repressed in the premigratory neural crest domain prior to EMT, and experimental overexpression of N-cadherin in the chick embryo suppresses EMT [48], whereas injection of adhesion-blocking antibodies triggers ectopic migration of NCC [49]. The loss of N-cadherin from the premigratory neural crest domain coincides with the induction of two to three different type II cadherins (cadherin switch in EMT), dependent on the species and the location to which the neural crest cells migrate.

The pathophysiological role of junction control

In the adult organism, EMT can be an element of cancer progression (see below) and of organ fibrosis, which can occur in various epithelial tissues such as kidney, liver, lung, and intestine. Organ fibrosis is basically a chronic inflammatory disease that is modulated by a multitude of inflammatory mediators. They cause loss of polarity and cell contact of epithelial cells of which most undergo apoptosis and some give rise to novel mesenchymal fibrotic cells [50]. TGF-β is an important factor in these events and a main inducer of Snail and thereby of the loss of E-cadherin, which supports EMT and disruption of epithelia. BMP-7 represents a potent inhibitor of TGF-β-induced EMT and one of its effects is the reversal of TGF-β-induced loss of E-cadherin [51].

Cerebral cavernous malformation (CCM) is a vascular dysplasia that affects mainly brain vessels with an incident of 0.5 % among humans. CCM lesions are characterized by enlarged irregular blood vessels that tend to hemorrhage. The disease is often caused by mutations in CCM-1, CCM-2, or CCM-3. Recently, it was shown that deletion of endothelial CCM-1 in mice led to endothelial mesenchymal transition (EndMT), which was caused by the upregulation of BMP-6 and TGF-β. VE-cadherin was strongly disorganized in vascular lesions, and N-cadherin was upregulated [52].

Endothelial junctions are generally very dynamic, and inflammatory processes stimulate vascular permeability for plasma proteins and the transit of leukocytes through endothelium and blood vessel wall. VE-cadherin is a major player in these processes [53], and tyrosine phosphorylation of different sites of the cytoplasmic domain of VE-cadherin regulates the two processes in selective ways in vivo [54].

The desmosomal cadherin desmocollins and desmogleins bind selectively to plakoglobin (not β-catenin), which forms the bridge to desmoplakin that in turn binds to intermediate filaments. Together with plakophilins and several other desmosome-associated proteins, clustering and lateral association of desmosomal cadherins is controlled. Auto-antibodies against desmogleins, which cause loss of adhesion between keratinocytes, leads to a skin blistering disease called pemphigus vulgaris [55]. Mutations in desmoglein-1 and desmoglein-4 and in desmocollin-3 have been associated with skin diseases and with hair loss [56–58]. Fifty percent of all patients with arrhythmogenic right ventricular cardiomyopathy harbor mutations in either one of the two major myocardial desmosomal cadherin desmoglein-2 and desmocollin-2 or in genes for the associated cytosolic proteins plakoglobin, plakophilin, and desmoplakin [59].

Relevance of the cadherin catenin complex for tumor development

The major components of the cadherin catenin complex are important for the control of tumor development. E-cadherin [60, 61] and α-catenin [62] represent tumor suppressors, and β-catenin can act as an oncogene [63]. Different mechanisms of inactivation of E-cadherin have been described in human cancer ranging from loss of heterozygosity, inherited and somatic mutations, defects in protein processing, increased promoter methylation, and induction of transcriptional repressors such as [64]. In several cases, a typical switch in the expression from E-cadherin to either N-cadherin or P-cadherin has also been described. As exceptions, in some tumors, E-cadherin is not downregulated but even overexpressed such as in epithelial ovarian cancers and in inflammatory breast cancer [64]. Besides E-cadherin,

also, α-catenin acts as a tumor suppressor. It regulates the localization and transcriptional activity of Yap [65], an important factor of the Hippo pathway that is involved in contact inhibition of proliferation [66]. Indeed, α-catenin was identified as recurrently mutated in laryngeal squamous cell carcinoma patients [67].

Besides its essential function in the cadherin catenin complex, β-catenin is also a central component of the canonical wnt signaling pathway. In the absence of wnt, cytosolic pools of β-catenin are low due to a multiprotein complex consisting of the scaffolding protein adenomatous polyposis coli (APC) and Axin 1 and 2 (conductin) and the kinases glycogen synthase kinase 3β (GSK3) and casein kinase 1 (CK1). This complex triggers phosphorylation of β-catenin at serine/threonine sites which leads to ubiquitination and subsequent degradation. This is blocked upon wnt signaling, which leads to enhanced cytosolic levels of β-catenin. These enhanced levels allow β-catenin to interact with transcription factors of the TCF/LEF family [68–70] and modulate transcription of a large repertoire of genes. Loss of APC leads to higher levels of β-catenin and consequently β-catenin-modulated gene expression. The consequence is an imbalance of the expression of genes responsible for differentiation and proliferation, which leads to the destruction of tissue architecture and enhanced proliferation. Numerous inactivating mutations of APC have been described in humans that are the basis for sporadic colorectal cancers and familial adenomatous polyposis. In many cases without mutations in APC, mutations in β-catenin were found that rendered it resistant against degradation [71].

The catenin p120 has tumor suppressor function, since it stabilizes cadherin function. Loss of p120 would decrease cadherin adhesion and possibly enhance signaling via growth factor receptors. In addition, p120 can also be pro-tumorigenic by participating in signaling steps in the cytosol that are required for anchorage-independent growth [72].

Concluding remarks

The switch in cadherin expression during EMT illustrates that a given repertoire of cadherins in a cell determines cell fate and cell behavior. How the loss of certain cadherins contributes to EMT and epithelial cell delamination and invasion is understood in some detail. Yet, how the gain of certain cadherins supports cell invasion and tumor development will be an interesting topic to study in the future. Other interesting aspects of cadherin function are the potential roles in cognitive disorders and neurosensory diseases as has been suggested for some protocadherins [73]. In addition, the molecular mechanisms of cytoskeleton-anchorage, cadherin clustering and of cadherin-modulated signal transduction will continue to be major topics of cadherin research in the future.

IMPLICATIONS AND INDICATIONS

Implications of cadherins in diseases

Cancer	
Mutations that lead to a loss of E-cadherin. In several cases, other cadherins (e.g., N-cadherin, P-cadherin) are upregulated	Reviewed in [64]
Mutations in α (N)-catenin and α (T)-catenin frequently found in laryngeal squamous cell carcinoma	[67]
Mutations in APC	[71]
Mutations in β-catenin	[71]
Renal fibrosis	
E-cadherin is downregulated in kidney fibrosis by TGF-β, which leads to EMT and supports fibrosis	[51]
Cerebral cavernous malformations	
Caused by mutations in CCM proteins. Defects in CCMs lead to TGF-β-mediated EndMT accompanied by irregular distribution of VE-cadherin and upregulation of N-cadherin in endothelial cells	[52]
Pemphigus vulgaris	
Autoimmune disease directed against Dsg1 and Dsg3	[55]
Skin disease and hair loss	
Various such diseases in humans are related to mutations in Dsg1, Dsg4, and Dsc3	[56–58]
Arrhythmogenic cardiomyopathy	
Associated with mutations in Dsg2 and Dsc2 in humans	Reviewed in [59]
Cognitive disorders and neurosensory diseases	
Several protocadherins are discussed as being relevant	Reviewed in [73]

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